IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Heribert SCHMITT-WILLICH et al. :

Serial No.: 08/319,357 :

Filed: October 6, 1994 :

Group Art Unit: 2203

Examiner: L. Chapman

#36

For: DERIVATIZED DTPA COMPLEXES, PHARMACEUTICAL AGENTS CONTAINING THESE COMPOUNDS, THEIR USE, AND PROCESSES FOR THEIR PRODUCTION

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

I, Andreas Mühler, being duly warned declare that:

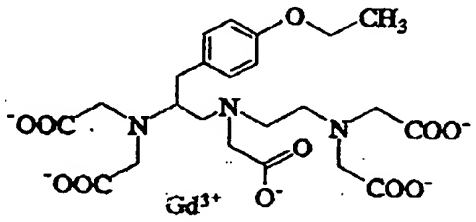
I am a citizen of Germany, presently residing at 24 Nimitz Road, Wayne, New Jersey 07470, with a permanent residence at Fontanestrasse 23A, 15366 Neuenhagen, Germany.

I possess the degree of Medical Doctorate, having studied medicine at Humboldt-University, Berlin Germany.

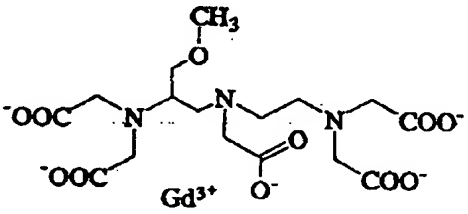
Since June 1, 1992, I have been employed as a scientist by Schering Aktiengesellschaft, Berlin, Germany, and am presently a clinical scientist at Berlex Laboratories, Inc., Wayne, New Jersey, a Schering AG subsidiary.

Under my supervision, excretion experiments were conducted comparing the biliary excretion of gadolinium methoxymethyl and Gd-ethoxybenzyl-DTPA (Gd-EOB). The structures of these two chelate complexes are shown below:

Gd-EOB



Gd-methoxymethyl DTPA



Excretion

Using the technique of inductively coupled plasma atomic emission spectrometry (ICP-AES) which is very sensitive for the quantitative measurement of lanthanide ions including gadolinium (detection limit of 65 nmol Gd/L), the following excretion data were obtained in rats (Wistar-Han, 140-160 g).

Following single intravenous administration of 0.1 mmol Gd/kg body weight, biliary excretion of test substances was measured in anesthetized animals by collection of bile by catheterization of the bile duct up to 4 h after administration. Additionally, the gadolinium dose remaining in the liver at 4 hours following intravenous injection was measured after sacrificing the animals. Three animals per test substance were investigated. The excretion test results and the remaining dose in the liver are shown in the following table:

Excretion (% injected dose)	Gd-methoxymethyl DTPA	Gd-ethoxybenzyl DTPA
Urine 0-2 h	68.1	19.0
Urine 2-4 h	7.5	3.9
Urine Total	75.6	22.9
Bile 0-2 h	0.6	62.5
Bile 2-4 h	0.2	5.7
Bile Total	0.8	68.2
Liver 4 h p.i.	0.6	0.9
Total	77.0	91.8

As can be seen from the above, in the time period of 0-4 hours, less than 1% of the administered dose of Gd-methoxymethyl DTPA was excreted via the biliary system. Conversely, in the same time period, more than 68% of Gd-EOB was excreted by the biliary system. The biliary excretion of Gd-methoxymethyl DTPA is extremely low in comparison to that of Gd-EOB.

Thus, the higher biliary excretion of the EOB chelate complex demonstrates unexpected beneficial and advantageous results for using the EOB chelate complex in magnetic resonance imaging of the liver and the biliary system.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

April 18, 1996
Date

Andreas Mühler

BPH:kdp128:sch1412.dc3